Remarks

This Amendment is responsive to the Office Action mailed on June 21, 2000 (Paper No. 8). Entry of this Amendment and reconsideration of the subject application in view thereof are respectfully requested.

Claims

Claims 1-40 were pending and these claims are rejected.

Claims 1, 4, 8-10, 18, 19, 23-25 and 32-40 have been amended to more clearly define the invention. Applicant respectfully submits that no new matter is added by these amendments.

Any alterations made to the claims were made solely to expedite or otherwise facilitate prosecution and were not made nor should they be construed to have been made to overcome any issue of unpatentability of the prior claims.

Specification

The Examiner has noted that the application fails to comply with requirements of 37 CFR §§1.821-1.825 because the "specification and drawings disclose nucleotide sequences which have not been identified by an appropriate SEQ ID NO." Accordingly, the specification has been amended to identify each disclosed sequence by an appropriate SEQ ID NO. The Application contains sequences with SEQ ID NOS: 1-68 which are disclosed in the "Sequence Listing" as filed.

The specification has been objected to because a trademark designation in the context of reciting "cytofectin" in the specification has not been provided. Applicant respectfully submits that with the entry of this amendment this requirement is satisfied.

The specification has also been amended to correct obvious typographical errors.

Applicant respectfully submits that no new matter is introduced by these amendments.

Rejections Under 35 U.S.C. § 112 Second Paragraph

The Examiner rejected claims 1-40 under 35 U.S.C. § 112, second paragraph. Applicant has made a number of clarifying amendments which retain a focus on the subject matter of the invention and address a number of the Examiner's concerns as well. At the same time, however,

some aspects of the rejection are not well taken. Accordingly, this ground of rejection are respectfully requested.

Claim 1 stood rejected based on the assertion that there is insufficient antecedent basis for the term "the stable genetic modifications" in this claim. Applicant respectfully submits that claim 1 as amended has sufficient antecedent basis to this term. Reconsideration and withdrawal of this ground of rejection are respectfully requested.

Claims 1 and 18 - "locations", "effective amount", "chimeric RNA-DNA oligonucleotide" and "naturally expressed"

Claims 1and 18 stood rejected as indefinite in their recitation of "locations", "effective amount", "chimeric RNA-DNA oligonucleotide" and "naturally expressed" Specifically, as to "locations" Applicant respectfully submits that claim 1 as amended clarifies that this refers to skin and makes method steps to relate back to the preamble. As to "effective amount", claim 1 as amended clarifies that this refers to an amount of a composition sufficient to bring about a stable genetic modifications in the selected gene. As to "chimeric RNA-DNA oligonucleotide" Applicant respectfully submits that the limitations which may apply to these oligonucleotides are sufficiently detailed in the specification and in the published research articles to satisfy those of ordinary skill in the field. Notwithstanding, solely to facilitate the prosecution, Applicant has amended these claims. The Examiner repeatedly averred in the Office Action that the only RDOs explicitly disclosed are those containing T-loop containing "dumbbell" structures. Upon reflection, Applicant suggests the phrase "double hairpin structure with pyrimidine loops" which phrase it believes (instead of a "T-loop containing 'dumbbell' structures") is consistent with the disclosure in the specification and the goal sought by the Examiner. Therefore, this phrase has been recited in the relevant claims. Accordingly, it is respectfully submitted that the these claims, as amended, are not indefinite and requests withdrawal of this ground of rejection.

Claims 8 and 23 "the region"

Claims 8 and 23 stood rejected based on the assertion that these claims are indefinite in their recitation of "the region". Applicant respectfully submits that claims 8 and 23 as amended no longer recite this language, thereby obviating this ground of rejection.

Claims 8 and 23 - "the site of modification"

Claims 8 and 23 stood rejected based on the assertion that there is insufficient antecedent basis for the term "the site of modification" in claims 8 and 23. Applicant respectfully submits that claims 8 and 23 have been amended to address the insufficient antecedent basis to this term. Reconsideration and withdrawal of the rejection based on this ground are respectfully requested.

Claims 8-10 and 23-25 - "nuclease protected"

Claims 8-10 and 23-25 stood rejected based on the assertion that these claims are indefinite in their recitation of "nuclease protected". Applicant respectfully submits that the relevant claims have been amended to more clearly claim the subject matter of the invention. Further, it is respectfully submitted that the guidance in the specification, for example, at page 32, line 10 through page 34, line 20 provides sufficient description of what nucleases the oligonucleotide is resistant to and whether first and second strings are contiguous to sufficiently appraise those of ordinary skill in the art. Reconsideration and withdrawal of this rejection are respectfully requested.

Claims 9 and 24 - "the two strands" and "the site of modification"

Claims 9 and 24 stood rejected based on the assertion that there is insufficient antecedent basis for the terms "the two strands" and "the site of modification" in these claims. Applicant respectfully submits that, with the entry of the present amendment, this ground of rejection no longer applies.

Claims 9, 10, 24 and 25 - "has nucleotides in the first string and second strings that are"

Claims 9, 10, 24 and 25 stood rejected based on the assertion that these claims are indefinite in their recitation of "has nucleotides in the first string and second strings that are" Applicant respectfully submits that, with the entry of the present amendment, this ground of rejection no longer applies. Reconsideration is respectfully requested.

Claims 10 and 25 - "the same number of deoxynucleotides".

Claims 10 and 25 stood rejected based on the assertion that these claims are indefinite in their recitation of "the same number of deoxynucleotides". Applicant respectfully submits that, with the entry of the present amendment, this ground of rejection is no longer applicable. Reconsideration is respectfully requested.

Claim 32 - "treatment"

Claim 32 stood rejected based on the assertion that these claims is indefinite in its recitation of "treatment". Applicant respectfully submits that claim 32 as amended clarifies that the oligonucleotide causes a mutation in the selected skin gene which mutation leads to the skin disorder. Reconsideration and withdrawal of this rejection are respectfully requested.

Claims 34-39 - "the method"

Claims 34-39 stood rejected based on the assertion that these claims are indefinite in their recitation of "[t]he method". Claims 34-39 as amended no longer recite "the method". Reconsideration and withdrawal of this ground of rejection are respectfully requested.

Claim 40 - "locations"

Claim 40 stood rejected based on the assertion that this claim is indefinite in its recitation of "locations". Claim 40 as amended clarifies that "locations" refer to the locations of the mammalian skin. Reconsideration is respectfully requested.

Accordingly, Applicant respectfully submits that withdrawal of the rejections under 35 U.S.C. §112, second paragraph is in order.

Rejections Under 35 U.S.C. §112, First Paragraph

Claims 2-7, 19, 32, 33 and 40 stood rejected under 35 U.S.C. § 112, first paragraph for lacking sufficient written description in the specification *i.e.*, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the specification was filed, had possession of the claimed invention. Applicant respectfully disagrees as supported by the following discussion.

The Examiner contended, among other things, that there is no evidence that applicant was in possession of gene sequences for anything other than Tyr, COL17A1 and KRT17 and the specification does not provide an adequate written description concerning the mutations which form the basis for designing the RDOs to target the broad range of genes recited in claims 4, 19, and 33. These contentions are not well taken. Applicant respectfully submits that it is not claiming the sequences for these genes recited in claims 4, 19, and 33. Further, the specification provides scientific journal article citations to these genes as listed in Table 1 on pages 51 and 52 of the specification. These articles which contain information on gene sequences and/or gene

mutations which articles are incorporated by reference. MPEP §2163.07(b). Further, the nucleic acid sequences for these genes are available in the public domain databases (e.g. GenBank). For example, following are GenBank accession numbers for some of the genes listed in Table 1 of the specification: #4502960 for COL7A1, #6678659 for LAMA3, #4557712 for LAMB3, #9845499 for LAMC2, #4557674 for ITGAG, #4504768 FOR ITGB4, #4505876 for PLEC1. The specification also teaches a routine, art recognized, method of designing RDOs. These teachings form the basis for designing the RDOs to target all of the recited genes. The cited cases do not apply to the present case. For instance, in *Fiers v. Revel*, the court found lack of written description for the nucleic acids claimed therein because the application at issue in that case did not disclose the nucleotide sequence for the claimed beta-IF which is not the case here, i.e., applicant is not claiming the gene sequences, for example, of Tyr, COL7A1, LAMA3, DSG3 and BPAG2, etc. Considering the specification's disclosure of gene sequences or references containing information as to the gene sequences and/or the gene mutations, structure of RDOs and publicly available gene sequence information taken in view of the general level of knowledge and skill in the art, one skilled in the art would recognize from the disclosure that Applicant was in possession of the invention at the time this application was filed.

Another asserted ground for this rejection was that the claims recited a broader genus of RDOs, not just the "RDOs containing T-loop containing "dumbbell" structures. Applicant disagrees. The specification discloses specific RDO embodiments and define and limit the structural features of effective RDOs which features constitute a substantial portion of the genus such that one skilled in the art would be able to readily envisage other members of the genus. Under the law one is not required to describe every detail of his or her invention. *University of California v. Eli Lilly*, 119 F.3d 1559 (Fed. Cir. 1997).

As to the written description for the recitation of various animals in the claims, Applicant respectfully requests that, solely to facilitate prosecution and in no way acquiescing to the Examiner's rejection, it has elected to amend the claims at issue. Specifically, the claims are limited to mice and humans. In view of the above discussions and amendments, the pertinent claims, it is believed that the alleged grounds for this rejection have been obviated. Reconsideration and withdrawal of the rejection are respectfully requested.

The Examiner further rejected claims 1-40 under 35 U.S.C. § 112, first paragraph. The Examiner asserts that these claims are not enabled. Applicant respectfully traverses this rejection.

At the outset, Applicant respectfully submits that the specification is replete with teachings enabling a person skilled in the art to which the invention pertains, or with which it is most nearly connected, to make or use the invention commensurate with the scope of these claims. However, without conceding the validity and solely to facilitate prosecution of this rejection, Applicant has amended claims so as to limit claims to mice and humans. Accordingly, the following discussion of the enablement rejection is limited to the amended claims.

The Examiner on pages 9-10 asserted that "Applicant has provided working examples which demonstrate that RDOs can be used to provide partial genetic correction.. Applicant has not provided any working examples which support the notion that insertions or deletions can be similarly introduced in skin". Applicant respectfully submits that compliance with 35 U.S.C. § 112, first paragraph, does not turn on whether an examples is disclosed. MPEP §2164.02. Notwithstanding, Application provides, as acknowledged by the Examiner, working examples with respect to certain embodiments of the invention. To satisfy the enablement requirement, Applicant need not describe all actual embodiments *SRI Int'l v. Matsuhita*, 775 F.2d 1107 (Fed. Cir. 1985).

As to Stephenson (JAMA 281(2):119-120, 1999) and Strauss (Nature Medicine, 4(3): 274-275, 1998), Applicant respectfully submits that the selected statements, including the Applicant's statements quoted by the Examiner, from these references do not concern modification of genes in cells of a <u>human skin in vivo</u> using chimeric RDOs. For example, Applicant's statements in Stephenson article (at p.120, left column, last paragraph) relate to the ability of RDO's to modify genes in cells in vitro, non in vivo. Applicant has shown that gene modification in skin cells in vivo can be predictably achieved by practicing the claimed invention. Further, as described in the specification, for example, at page 15, that a very high frequency of gene modification was achieved in vivo in contrast to that in vitro.

Stephenson and Strauss also comment on the work done in other laboratories, but these laboratories focused on gene modifications in hapatocytes, liver and epithelial cells not in skin tissue. Thus, these references do not comment on the ability of RDO to correct or modify genes

in cells of skin in vivo. It is well known that skin is rapidly renewing tissues in a process of constant regeneration. Reports on cell kinetics in mouse and human skin in vivo show that the proliferative process of skin is achieved by epidermal stem cells. RDO is capable of epidermal stem cell gene modifications. The expansion of such cells would result in an apparent high level of gene conversion in epidermis. Hence, gene modification even in few stem cells would result in an apparent high level of gene modification as these stem cells expand and repopulate epidermis. Thus, gene modification by RDO in human skin in vivo is different from other reports relied on by the Examiner because of the high epidermal turnover. Therefore, lack of routine success with gene modification by applying RDO in in vitro cells or tissues such as liver does not support a conclusion that the claimed invention which relates to the genetic modification in skin in vivo is nonenabled.

As to the similarities between human and mouse skin cell types, Applicant respectfully submits that the gene modifications and phenotypic changes obtained with the mouse system can also be achieved in humans because of similarity of cell types in mouse and human; in fact, mouse skin provided a valuable animal model for human skin diseases. (See, Coulombe et al, 1991, Cell 66:1301-1311, a copy of which is enclosed hereby as Exhibit 1.)

To require further proof would place the Applicant in the position of having to produce full scale clinical studies with humans which would be contrary to law. *In re Brana,* 51 F.3d 1560, 1568 (Fed. Cir. 1995).

Based on the above arguments, Applicant respectfully submits that the specification sufficiently teaches the instant invention, as presently claimed, so that one skilled in the art can practice the invention as claimed without the burden of undue experimentation. Reconsideration is respectfully requested.

In view of the foregoing and the amendments presented herein, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of claims under 35 U.S.C. §112, first paragraph.

Conclusion

Applicant believes this response to be a full and complete response to the Office Action. Accordingly, favorable reconsideration in view of this response and allowance of the pending claims are earnestly solicited.

Respectfully submitted,

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APPENDIX: Claims pending in application Serial No. 09/473,872 after the entry of the amendment filed on December 20, 2000:

1. A method of modifying a selected gene in cells of a human skin in vivo which comprises delivering to said cells at one or more locations of the human skin an effective amount of a composition sufficient to bring about stable genetic modifications in the selected gene wherein the composition comprises a chimeric RNA-DNA oligonucleotide and a pharmaceutically acceptable carrier such that said genetic modifications are made to the selected gene which result in phenotypic changes at said locations of the human skin wherein the chimeric RNA-DNA oligonucleotide has a double hairpin structure with pyrimidine loops.

2. The method of claim 1, wherein the stable genetic modification is in an epidermal fragility disorder gene.

3. The method of claim 1, wherein the stable genetic modification is in a keratinization disorder gene.

4. The method of claim 1, wherein the selected gene is tyrosinase, COL7A1, LAMA3, LAMB3, LAMC2, COL17A1, ITGA6, ITGB4, PLEC1, KRT5, KRT14, PKP1, KRT1, KRT10, KRT9, KRT16, LOR, KRT2e, KRT6a, KRT 16, KRT 17, STS, TGM1, GJB2, GJB3, ATP2A2, DSP, DSG1, HR, hHB1, hHB6, PAX3, TYR, TYRP-1, OCA2, OA1, MITF, HPS, FECH, UROS, URO-D, XPA, XPB, XPC, XPD, XPG, CSB, PTC, STK11/LKB1, PTEN, PTEN, XPB, XPD, WHN, GLA, ATM, ENG, ALK-1, PPO, BPAG2, or DSG3 gene.

5. The method of claim 1, wherein the selected gene is tyrosinase gene.

6. The method of claim 1, wherein the selected gene is COL7A1 gene.

7. The method of claim 1, wherein the selected gene is KRT17 gene.

8. The method of claim 1, wherein the chimeric RNA-DNA oligonucleotide comprises:

(a) a first string of nucleotides wherein the first string is made of at least four contiguous deoxyribonucleotides flanked on each side by at least nine ribonucleotides; and

(b) a second string of deoxyribonucleotides that is fully complementary to the first string of nucleotides, and

wherein the chimeric RNA-DNA oligonucleotide is, nuclease protected, and wherein the chimeric RNA-DNA oligonucleotide has contiguous nucleotides in each of the first and second strings that are fully complementary to a segment of DNA of the selected gene except that the first string has one mismatching deoxyribonucleotide in said contiguous deoxyribonucleotides that defines a site of modification in the selected gene.

9. The method of claim 1, wherein the chimeric RNA-DNA oligonucleotide comprises:

(a) a first string of nucleotides wherein the first string is made of at least 20 ribonucleotides; and

(b) a second string of deoxyribonucleotides having the same number of deoxyribonucleotides as in the first string of nucleotides, wherein the second string is fully complementary to the first string of nucleotides except that the second string has a deoxyribonucleotide that forms a mismatched base pair with the corresponding nucleotide in the first string, and

wherein the chimeric RNA-DNA oligonucleotide is nuclease protected, and wherein the chimeric RNA-DNA oligonucleotide has contiguous nucleotides in each of the first and second strings that are fully complementary to a segment of DNA of the selected gene except that the deoxyribonucleotide in the second string also forms a mismatched base pair with the corresponding deoxyribonucleotide in the DNA strand of the selected gene which mismatched base pair defines a site of modification in the selected gene.

10. The method of claim 1, wherein the chimeric RNA-DNA oligonucleotide comprises:

(a) a first string of nucleotides wherein the first string is made of at least four contiguous deoxyribonucleotides flanked on each side by at least nine ribonucleotides; and

(b) a second string of deoxyribonucleotides that is fully complementary to the first string of nucleotides, and

wherein the chimeric RNA-DNA oligonucleotide is nuclease protected, and wherein the chimeric RNA-DNA oligonucleotide has contiguous nucleotides in each of the first and second strings that are fully complementary to a segment of DNA of the selected gene except that the first and second strings have one, two or four pairs of nucleotide insertions or deletions that defines a site of modification in the selected gene.

11. The method of claim 1, wherein the stable genetic modification is correction of a mutation.

12. The method of claim 11, wherein the mutation is a point mutation or a frame shift mutation.

13. The method of claim 1, wherein the stable genetic modification is generation of a mutation.

14. The method of claim 13, wherein the mutation is a point mutation or a frame shift mutation.

15. The method of claim 13, wherein the mutation is a dominant mutation.

16. The method of claim 1, wherein said phenotypic changes include the correction of a skin disorder.

17. The method of claim 1, wherein said phenotypic changes include the correction of albinism, an epidermal fragility disorder or a keratinization disorder.

18. A method of modifying a selected gene in cells of an animal skin in vivo which comprises delivering to said cells at one or more locations of the animal skin an effective amount of a composition comprising a chimeric RNA-DNA oligonucleotide having a double hairpin structure with pyrimidine loops and a pharmaceutically acceptable carrier such that the stable genetic modifications are made to the selected gene which result in phenotypic changes at said locations of the animal skin, wherein the animal is a mouse.

19. The method of claim 18, wherein the selected gene is tyrosinase, COL7A1, LAMA3, LAMB3, LAMC2, COL17A1, ITGA6, ITGB4, PLEC1, KRT5, KRT14, PKP1, KRT1, KRT10, KRT9, KRT16, LOR, KRT2, KRT6, KRT 16, KRT 17, STS, TGM1, GJB2, GJB3, ATP2A2, DSP, DSG1, HR, hHB1, hHB6, PAX3, TYR, TYRP-1, OCA2, OA1, MITF, HPS, FECH, UROS, URO-D, PPO, XPA, XPB, XPC, XPD, XPG, CSB, PTC, STK11/LKB1, PTEN, PTEN, XPB, XPD, WHN, GLA, ATM, ENG, ALK-1, a cytokine BPAG2 or DSG3 gene.

20. The method of claim 18, wherein the selected gene is tyrosinase gene.

21. The method of claim 18, wherein the selected gene is COL7A1 gene.

22. The method of claim 18, wherein the selected gene is KRT17 gene.

23. The method of claim 18, wherein the chimeric RNA-DNA oligonucleotide comprises:

(a) a first string of nucleotides wherein the first string is made of at least four contiguous deoxyribonucleotides flanked on each side by at least nine ribonucleotides; and

(b) a second string of deoxyribonucleotides that is fully complementary to the first string of nucleotides, and

wherein the chimeric RNA-DNA oligonucleotide is nuclease protected, and wherein the chimeric RNA-DNA oligonucleotide has contiguous nucleotides in each of the first and second strings that are fully complementary to a segment of DNA of the selected gene except that the first string has one mismatching deoxyribonucleotide in said contiguous deoxyribonucleotides that defines a site of modification in the selected gene.

24. The method of claim 18, wherein the chimeric RNA-DNA oligonucleotide comprises:

(a) a first string of nucleotides wherein the first string is made of at least 20 ribonucleotides; and

(b) a second string of deoxyribonucleotides having the same number of deoxyribonucleotides as in the first string of nucleotides, wherein the second string is fully complementary to the first string of nucleotides except that the second string has a deoxyribonucleotide that forms a mismatched base pair with the corresponding nucleotide in the first string to make the genetic modifications in the selected gene, and

wherein the chimeric RNA-DNA oligonucleotide is nuclease protected, and wherein the chimeric RNA-DNA oligonucleotide has contiguous nucleotides in each of the first and second strings that are fully complementary to a segment of DNA of the selected gene except that the deoxyribonucleotide in the second string also forms a mismatched base pair with the corresponding deoxyribonucleotide in the DNA strand of the selected gene which mismatched base pair defines a site of modification in the selected gene.

25. The method of claim 18, wherein the chimeric RNA-DNA oligonucleotide comprises:

(a) a first string of nucleotides wherein the first string is made of at least four contiguous deoxyribonucleotides flanked on each side by at least nine ribonucleotides; and

(b) a second string of deoxynribonucleotides that is fully complementary to the first string of nucleotides, and

wherein the chimeric RNA-DNA oligonucleotide is nuclease protected, and wherein the chimeric RNA-DNA oligonucleotide has nucleotides in each of the first and second strings that

are fully complementary to a segment of DNA of the selected gene except that the first and second strings have one, two or four pairs of nucleotide insertions or deletions that defines a site of modification in the selected gene.

26. The method of claim 18, wherein the stable genetic modification is correction of a mutation.

27. The method of claim 26, wherein the mutation is a point mutation or a frame shift mutation.

28. The method of claim 18, wherein the stable genetic modification is generation of a mutation.

29. The method of claim 28, wherein the mutation is a point mutation or a frame shift mutation.

30. The method of claim 28, wherein the mutation is a dominant mutation.

31. The method of claim 18, wherein said phenotypic changes include the correction of albinism, an epidermal fragility disorder or a keratinization disorder.

32. An animal model having a skin disorder at one or more locations of its skin wherein the skin disorder is a result of a treatment at said locations with a composition comprising a chimeric RNA-DNA oligonucleotide having a double hairpin structure with pyrimidine loops targeted to a selected skin gene, said oligonucleotide thereby causing a mutation in the selected skin gene which mutation leads to the skin disorder, wherein the skin disorder is an epidermal fragility disorder, a keratinization disorder or albinism disorder.

33. The animal model of claim 32, wherein the selected skin gene is Tyr, COL7A1, LAMA3, LAMB3, LAMC2, COL17A1, ITGA6, ITGB4, PLEC1, KRT5, KRT14, PKP1, KRT1, KRT10, KRT9, KRT16, LOR, 1998, KRT2e, KRT6a, KRT 16, KRT 17, STS, TGM1, GJB2, GJB3, ATP2A2, DSP, DSG1, HR, hHB1, hHB6, PAX3, TYR, TYRP-1, OCA2, OA1, MITF, HPS, FECH, UROS, URO-D, PPO, XPA, XPB, XPC, XPD, XPG, CSB, PTC, STK11/LKB1, PTEN, PTEN, XPB, XPD, WHN, GLA, ATM, ENG, ALK-1, a cytokine BPAG2 or DSG3 gene.

34. The animal model of claim 33, wherein the selected gene is Tyr gene.

35. The animal model of claim 33, wherein the selected gene is COL7A1 gene.

36. The animal model of claim 33, wherein the selected gene is KRT17 gene.

37. The animal model of claim 32, wherein the skin disorder is due to generation of a mutation in the selected skin gene.

38. The animal model of claim 37, wherein the mutation is a point mutation or a frame shift mutation.

39. The animal model of claim 37, wherein the mutation is a dominant mutation.

40. A method of correcting a mutation in a tyrosinase gene in cells of a mammalian skin in vivo which comprises delivering to said cells at one or more locations of the mammalian skin an effective amount of a composition comprising a Tyr-A RNA-DNA oligonucleotide for causing stable genetic correction in the tyrosinase gene and a pharmaceutically acceptable carrier such that the correction results in restoration of tyrosinase enzyme activity at said locations of the mammalian skin, wherein the mammalian skin is selected from the group consisting of a human and a mouse.

INACTIVE TYROSINASE(ALBINO PHENOTYPE)

Phe Met Gly Phe Asn Cys Gly Asn Ser Lys Phe Gly Phe Gly Gly Pro [SEQ ID NO:1]

5'TTC ATG GGT TTC AAC TGC GGA AAC TCT AAG TTT GGA TTT GGG GGC CCA 3'[SEQ ID NO:2]

3'AAG TAC CCA AAG TTG ACG CCT TTG AGA TTC AAA CCT AAA CCC CCG GGT 5'[SEQ ID NO:3]

+

A.

T GCGCG ug acg ccu uuG ACA Tuc aaa ccu aa T

T T Tyr-A

T T [SEQ ID NO:4]

T CGCGC|AC TGC GGA AAC TGT AAG TTT GGA TT T

3'5'

↓

ACTIVE TYROSINASE(BLACK PHENOTYPE)

Phe Met Gly Phe Asn Cys Gly Asn Cys Lys Phe Gly Phe Gly Gly Pro [SEQ ID NO:5]

5'TTC ATG GGT TTC AAC TGC GGA AAC TGT AAG TTT GGA TTT GGG GGC CCA 3'[SEQ ID NO:6]

3'AAG TAC CCA AAG TTG ACG CCT TTG ACA TTC AAA CCT AAA CCC CCG GGT 5'[SEQ ID NO:7]

B.

T GCGCG ug acg ccu uuG AGA Tuc aaa ccu aa T

T T Tyr-B

T T [SEQ ID NO:8]

T CGCGC|AC TGC GGA AAC TCT AAG TTT GGA TT T

3'5'

FIG. 1